Sleep Medicine 15 (2014) 342–347

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Disturbances in melatonin secretion and circadian sleep–wake regulation in Parkinson disease

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ARTICLE INFO

Article history:
Received 9 July 2013
Received in revised form 27 September 2013
Accepted 15 October 2013
Available online 21 January 2014

Keywords:
Parkinson disease
Sleep disorders
Melatonin
Circadian
Dopamine
Actigraphy

ABSTRACT

Objective: Using salivary dim light melatonin onset (DLMO) and actigraphy, our study sought to determine if Parkinson disease (PD) patients demonstrate circadian disturbance compared to healthy controls. Additionally, our study investigated if circadian disturbances represent a disease-related process or may be attributed to dopaminergic therapy.

Methods: Twenty-nine patients with PD were divided into unmedicated and medicated groups and were compared to 27 healthy controls. All participants underwent neurologic assessment and 14 days of actigraphy to establish habitual sleep-onset time (HSO). DLMO time and area under the melatonin curve (AUC) were calculated from salivary melatonin sampling. The phase angle of entrainment was calculated by subtracting DLMO from HSO. Overnight polysomnography (PSG) was performed to determine sleep architecture.

Results: DLMO and HSO were not different across the groups. However, the phase angle of entrainment was more than twice as long in the medicated PD group compared to the unmedicated PD group ($U = 35.5$; $P = .002$) and was more than 50% longer than controls ($U = 130.0$; $P = .021$). The medicated PD group showed more than double the melatonin AUC compared to the unmedicated group ($U = 31$; $P = 0.001$) and controls ($U = 87$; $P = .001$). There was no difference in these measures comparing unmedicated PD and controls.

Conclusions: In PD dopaminergic treatment profoundly increases the secretion of melatonin. Our study reported no difference in circadian phase and HSO between groups. However, PD patients treated with dopaminergic therapy unexpectedly showed a delayed sleep onset relative to DLMO, suggesting dopaminergic therapy in PD results in an uncoupling of circadian and sleep regulation.

1. Introduction

Sleep–wake disturbances are gaining increased attention in patients with Parkinson disease (PD). Such symptoms are observed in over two-thirds of patients [1] manifesting with a range of features, including insomnia, rapid eye movement (REM) sleep behavior disorder, and excessive daytime somnolence [1]. In addition to impact on quality of life for patients and their caretakers [2], these symptoms have been linked to cognitive deficits [3,4] and the development of PD dementia [5].

Sleep–wake cycles are regulated by the circadian system, mainly from the hypothalamic suprachiasmatic nuclei (SCN), which controls the rhythm of melatonin synthesis in the pineal gland. Although circadian disturbance is well-recognized in Alzheimer disease [6], specific contributions from structures such as the SCN or pineal gland have not been established in PD. In PD there is widespread neuronal loss with neurotransmitter deficits across dopaminergic and nondopaminergic systems throughout the brainstem, basal forebrain, hypothalamus, and frontostriatal pathways [7–9]. In addition, it has been recognized that the anterior hypothalamus sends monosynaptic outputs to the lateral hypothalamus, overlapping wake-promoting orexin neurons [10]. Because the synchrony between sleep and the circadian system is

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http://dx.doi.org/10.1016/j.sleep.2013.10.016
1389-9457/

dependent on the dorsolateral hypothalamic nuclei [10], it has been proposed that increased orexin through abnormal signaling from the SCN is a potential mechanism for the deregulation of this interaction [11].

Circadian rhythm disturbances have previously been investigated in patients with PD, utilizing the serial measurement of plasma melatonin to determine the onset in the rise of melatonin levels. These studies have reported a circadian phase advance with an earlier onset time of melatonin secretion in patients treated with dopaminergic medication compared to untreated patients and age-matched healthy controls [12,13]. Furthermore increased melatonin secretion has been reported in PD patients who have developed levodopa (L-dopa)-related motor complications compared to patients without these complications and newly diagnosed untreated PD [14]. However, these studies did not control for the acute inhibitory effect of light exposure on melatonin synthesis [15]. Furthermore, these studies included small numbers of participants and took no account of the effects of age, disease duration, disease stage, or mood disturbances.

Thus it is clear that existing studies have employed invasive 24-h plasma sampling with some methodologic deficiencies. Work in non-PD cohorts has successfully utilized melatonin measurements derived from a noninvasive serial salivary sampling [16,17]. This approach has allowed the time of melatonin onset under dim light conditions, referred to as dim light melatonin onset (DLMO) to be determined as a measure of circadian phase and evening melatonin output level. The relationship between DLMO and habitual sleep-onset time (HSO) can be used as a measure of synchrony between the circadian system and the sleep–wake cycle [11].

In addition to the important role melatonin plays in affecting the light–dark regulation circadian rhythms, the sleep-promoting effect of melatonin has been subject to debate [18]. Initial studies using exogenous melatonin failed to show a sleep-promoting effect. However, this lack of effect now appears to be due to the short half-life of the melatonin preparation used and inadequate dosing [19]. Subsequent studies provide compelling evidence that melatonin does have a sleep-promoting effect via direct neuronal suppression (for review see [20]). Furthermore, a recent consensus statement from the British Association for Psychopharmacology has proposed melatonin as first-line therapy for insomnia in older adults [21]. Therefore, if melatonin secretion was altered by neuropathologic changes or by dopaminergic replacement therapy it may be contributing to the sleep–wake disturbance seen in PD.

To our knowledge, our study is the first to combine salivary DLMO, polysomnography (PSG), and wrist actigraphy to identify if PD patients demonstrate circadian disturbance compared to age-matched healthy controls. Furthermore, our study was conducted to elucidate if disturbances in melatonin secretion are associated with PD pathology or if they could be attributed to the use of dopaminergic therapy. We suggest that a greater understanding of these processes will aid the design of future treatment strategies.

2. Methods

2.1. Participants

Twenty-nine patients with PD and 28 age-matched controls were recruited from the Brain and Mind Research Institute PD Research Clinic, University of Sydney, Australia. Patients with a history of obstructive sleep apnea were excluded. All patients satisfied the UK PD Society Brain Bank criteria [22]. The patient group comprised 13 patients who were unmedicated and 16 who were treated with dopaminergic medication. Of these, 11 patients were on L-dopa monotherapy, three were on dopamine agonist monotherapy, and two were on L-dopa plus a dopamine agonist. Three of the unmedicated patients were taking an antidepressant agent (amitriptyline, venlafaxine, mirtazapine), and three of the patients medicated with dopaminergic replacement therapy were taking an antidepressant agent (mirtazapine, amitriptyline, duloxetine). One of the age-matched healthy controls was taking paroxetine.

2.2. Clinical assessment

Patients were assessed in their "on" state and L-dopa dose equivalents were calculated for dopaminergic medication [23]. Disease stage was rated on the Hoehn and Yahr scale [24] and motor severity was scored on section III of the Unified PD Rating Scale [25]. Disease duration was calculated from time since disease diagnosis and was matched between patient groups. No patients were demented as assessed by the Movement Disorders Society PD Dementia criteria [26] and no participants had a history of major depression. The Mini-Mental State Examination (MMSE) was recorded as a global measure of cognition [27] and depressive symptoms were self-rated using the Beck Depression Inventory-II (BDI-II) Scores of 0–13 were indicative of minimal depressive symptoms [28].

2.3. Sleep and circadian assessment

Participants completed sleep diaries and were required to wear a wrist actiwatch (Minimitter Actiwatch Spectrum) on the wrist less affected by tremor every day for 14 days prior to in-laboratory DLMO assessment. Actigraphy sleep-rest intervals and determination of the HSO were calculated using Actiware 5.0 software (Minimitter-Respironics Inc, Bend, Oregon) and Actiwatch Firmware, version 01.01.0007 (Minimitter-Respironics Inc, Bend, Oregon), in conjunction with manual scoring by an experienced sleep technician [29,30]. HSO was determined calculating the mean of sleep-onset times derived from actigraphy data over the 14-day sampling period and was corroborated by the sleep diary data. Participants then attended the chronobiology and sleep laboratory at the Brain and Mind Research Institute for overnight PSG followed by circadian phase assessment.

Nocturnal PSG recordings were performed in the laboratory 1–2 weeks prior to the circadian phase assessment. Nocturnal PSG recordings were collected on an ambulatory recording system (Compumedics Siesta, Melbourne, Vic, Australia) using the following electroencephalographic montage (C3–M2, O2–M1, Fz–M1, Pz–M2): two electrooculographic channels (left and right outer canthi) and electromyogram (submentalis). Electroencephalographic data were sampled at 250 Hz. Sleep stages were visually scored by an experienced sleep technician using standardized criteria [31]. While in the laboratory, participants were physiologically and behaviorally monitored under controlled conditions with fixed light levels (<50 one time during waking and <1 one time during scheduled sleep periods) and ambient temperature (24 ± 1 °C). The following sleep variables were calculated: total sleep time (minutes), percentage of time in REM, percentage of time in slow-wave sleep, sleep-onset latency (SOL) (minutes), latency to REM sleep (minutes), and wake after sleep onset (minutes).

For the in-laboratory circadian phase assessment, participants were asked to arrive 7 h prior to their HSO, to familiarize themselves with the laboratory setting and to ensure they were in a controlled posture for at least 30 min before the first sample was collected. Saliva samples were collected at 30-min intervals (Salivette, Sarstedt, Germany) from 6 h before HSO until 2 h after HSO, per previously published protocols [11,17]. During this assessment, participants were physiologically and behaviorally

monitored under controlled conditions with fixed light levels that were confirmed with measurement to be less than 30 lux and ambient temperature (24 ± 1 °C). Participants maintained a seated posture for at least 20 min before each sample collection. On the day of melatonin measurement while in the sleep laboratory, patients were asked to abstain from substances believed to affect melatonin or sleep (e.g., caffeine, turkey, bananas, tomatoes). To minimize the effect of eating food, dinner was provided in two halves which could be consumed during the interval between two nonconsecutive melatonin sample collections.

Melatonin was assayed in 200 μL of saliva by double-antibody radioimmunoassay according to the manufacturer's instructions (Cat No. RK-DSM2; Buhlmann Laboratories AG, Schonenbuch, Switzerland). The lowest detectable level of melatonin was 4.3 pM. The intra-assay coefficient of variation was <10% across the range of the standard curve. The interassay coefficient of variation was 15% at 19.5 pM and 12.3% at 177 pM.

The area under the melatonin curve (AUC) was calculated using the trapezoidal method for each participant over the entire 8-h sampling period [11]. To ensure that any potential difference in AUC was not due timing of the melatonin sampling, the AUC in the first hour post-DLMO and the average AUC post-DLMO was calculated for all participants. A threshold for melatonin was calculated as the mean of the first three readings plus two standard deviations (SD). The DLMO was identified as the point when the saliva melatonin reached this threshold and remained elevated for at least the next sampling time in accordance with previously published criteria [11,17]. The phase angle of entrainment (measured in minutes) was calculated by subtracting the DLMO time from the HSO time.

2.4. Standard protocols approvals, registrations, and patient consent

Approval for the study was obtained from the University of Sydney Human Research Ethics Committee (HREC 08-2008/11105) and all patients gave written informed consent.

2.5. Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS version 20, for IBM. Age was compared between the groups using a one-way analysis of variance. Gender was compared using a χ^2 test. Subsequent variables violated assumptions of normality. Nonparametric data were first analyzed using the independent samples Kruskal–Wallis analysis of variance to determine if group differences existed using an α level of .05. Subsequent post hoc comparisons between groups were assessed using the Mann–Whitney *U* test. Bonferroni correction was used for multiple comparisons.

3. Results

Of the 78 participants in our study, 16 had a sporadic melatonin profile without an apparent rise in melatonin (4 unmedicated PD, 7 medicated PD, and 5 controls). A further five did not register any melatonin concentrations over the 8-h sampling period (1 unmedicated PD, 2 medicated PD, and 2 controls). DLMO, phase angle of entrainment, and AUC could not be evaluated for these participants.

Demographic, clinical, and circadian data are presented in Table 1. Age, depressive symptoms, and MMSE scores did not differ across the three groups. On average there were minimal depressive symptoms and high MMSE scores. There was no significant difference between the number of participants taking antidepressant medication across the three groups ($\chi^2 = 4.0$; $P = .135$). The medicated and unmedicated patient groups were matched for disease duration and did not differ on measures of disease stage (Hoehn and Yahr) or motor severity (section III of the Unified PD Rating Scale).

DLMO and HSO were not different across the three groups. However, there was a significant difference across groups in the phase angle of entrainment ($\chi^2 = 10.6$; $P = .005$) (Table 1). As shown in Fig. 1, the medicated group had a longer phase angle compared to the unmedicated groups ($U = 35.5$; $P = .002$). The medicated group also had a longer phase angle compared to the healthy control group ($U = 130.0$; $P = .021$). There was no difference in this measure between the unmedicated group and controls.

As shown in Table 1, the melatonin AUC was significantly different across the three groups ($\chi^2 = 14.0$; $P = .001$). The medicated patient group had more than double the AUC compared to unmedicated PD ($U = 31$; $P = .001$) and controls ($U = 87$; $P = .001$), respectively (Figs. 2 and 3). However, there was no difference when comparing unmedicated patients and controls.

Table 1
Descriptive, neurology, sleep, and circadian rhythm data for patients and controls.

	Unmedicated PD mean ± SD $n = 13$	Medicated PD mean ± SD $n = 16$	Controls mean ± SD $n = 28$	Statistic	*P* value
Age (y)	64.8 ± 6.0	63.6 ± 9.8	68.3 ± 9.0	$F = 1.7$	.195
Beck Depression Inventory-II	8.2 ± 6.1	6.9 ± 3.1	5.1 ± 4.0	$\chi^2 = 3.9$	.142
MMSE	28.1 ± 2.1	28.8 ± 1.4	29.1 ± 1.2	$\chi^2 = 2.1$	.359
UPDRS-III	27.0 ± 13.9	28.5 ± 14.4	–	$U = 98.0$	.792
Hoehn and Yahr	2.0 ± 0.5	1.9 ± 0.5	–	$U = 97.5$	.742
Disease duration (y)	1.0 ± 0.8	1.8 ± 1.3	–	$U = 63.0$	.072
L-dopa dose equivalent (mg)	–	420.3 ± 195.4	–		–
Total sleep time (min)	406.3 ± 38.7	393.9 ± 60.6	392.0 ± 50.7	$\chi^2 = 0.4$	.435
Slow-wave sleep (%)	16.9 ± 13.2	18.8 ± 12.0	16.4 ± 10.1	$\chi^2 = 0.6$	.735
REM sleep (%)	20.7 ± 5.9	21.6 ± 5.6	20.6 ± 5.3	$\chi^2 = 0.2$	.929
Sleep-onset latency	30.2 ± 22.1	14.8 ± 12.7	15.8 ± 14.0	$\chi^2 = 6.4$	.041
REM latency (min)	94.1 ± 71.0	78.8 ± 42.7	68.0 ± 23.4	$\chi^2 = 0.1$	.970
WASO (min)	86.00 ± 84.6	59.8 ± 51.2	96.8 ± 96.8	$\chi^2 = 1.1$	.580
DLMO (h:min)	20:58 ± 00:76	20:08 ± 00:78	20:58 ± 00:86	$\chi^2 = 3.1$	.210
HSO (h:min)	22:02 ± 00:56	22:46 ± 00:53	22:41 ± 00:51	$\chi^2 = 5.1$	.079
Entrainment phase angle (min)	65 ± 68	159 ± 72	103 ± 74	$\chi^2 = 10.6$	.005
AUC (pM)	124.9 ± 82.0	317.0 ± 175.2	146.7 ± 112.7	$\chi^2 = 14.0$	.001
AUC 1-h post-DLMO (pM)	26.4 ± 11.6	39.2 ± 15.7	24.9 ± 12.8	$\chi^2 = 10.6$	.005
AUC post-DLMO (pM/sample)	20.3 ± 12.3	32.7 ± 15.8	19.2 ± 12.6	$\chi^2 = 8.8$	.012

Abbreviations: PD, Parkinson disease; SD, standard deviation; y, years; MMSE, Mini-Mental State Examination; UPDRS-III, Unified Parkinson Disease Rating Scale Section III; L-dopa, levodopa; min, minutes; REM, rapid eye movement; WASO, wake after sleep onset; h:min, hours and minutes; DLMO, dim light melatonin onset; HSO, habitual sleep-onset time; AUC, area under the melatonin curve.

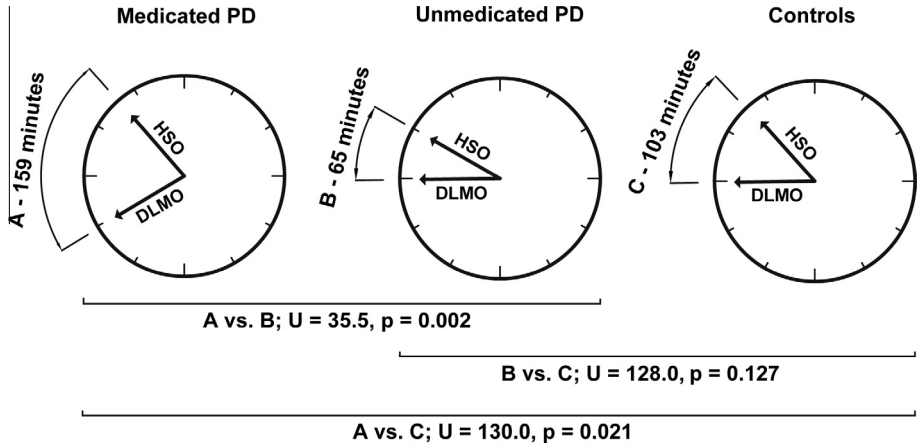

Fig. 1. Entrainment phase angle, habitual sleep-onset time (HSO), and dim light melatonin onset (DLMO). A graph demonstrating the longer entrainment phase angle (minutes) reported in patients with Parkinson disease (PD) who were medicated with dopaminergic replacement therapy compared to unmedicated patients with PD and healthy age-matched controls, respectively. The entrainment phase angle is calculated by subtracting the DLMO from the HSO measured in minutes.

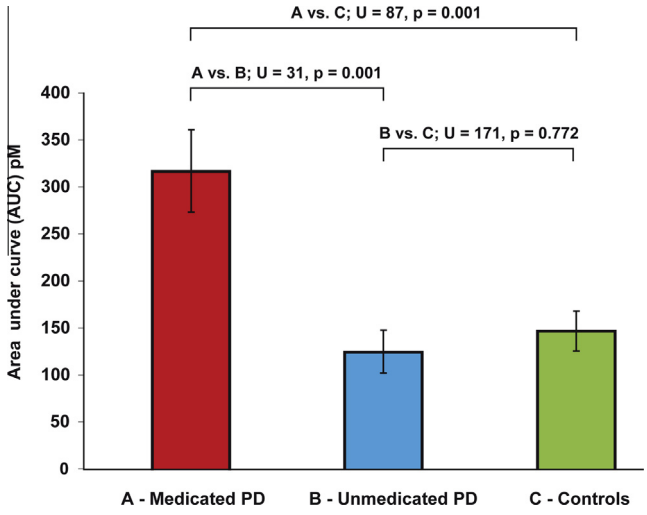

Fig. 2. Area under the melatonin curve (AUC) (pM). A chart depicting the increased AUC (mean ± standard error) reported in patients with Parkinson disease (PD) who were medicated with dopaminergic replacement therapy compared to unmedicated patients with PD and healthy age-matched controls, respectively. The melatonin curve was created for each participant by collecting melatonin levels every 30 min over the 8-h sampling period. The AUC was calculated using the trapezoidal rule.

To ensure that the increased AUC noted in the medicated group compared to unmedicated PD and controls, respectively, was not due to an error in the window of the melatonin curve sampled, melatonin data were plotted for all participants over the 8-h sampling period (Fig. 3; panel A). Furthermore, the average AUC 1 h post-DLMO and the average AUC post-DLMO was calculated. For the medicated PD group, the AUC 1 h post-DLMO was significantly higher than both unmedicated PD groups (39.2 [SD, 15.7] vs 26.4 [SD, 11.6]; $U = 54$; $P = .028$) and controls (39.2 [SD, 15.7] vs 24.9 [SD, 12.8]; $U = 109$; $P = .005$) (Fig. 3; panel B). Similarly the average AUC post-DLMO was significantly higher in the medicated PD group compared to both the unmedicated PD group (32.7 [SD, 15.8] vs 20.3 [SD, 12.3]; $U = 50$; $P = .018$) and controls (32.7 [SD, 15.8] vs 19.2 [SD, 12.6]; $P = .002$).

SOL was noted to be different between the groups ($\chi^2 = 6.4$; $P = .041$), with the medicated PD group reporting the lowest value of 14.8 min (SD, 12.7). However, this result was not sustained in a post hoc analysis comparing unmedicated PD to medicated PD (30.2 [SD, 22.1] vs 14.8 [SD, 12.7]; $U = 41.5$; $P = .022$), medicated PD to controls (14.8 [SD, 12.7] vs 15.8 [SD, 14.0]; $U = 196$; $P = .915$), and unmedicated PD to controls (30.2 [SD, 22.1] vs 15.8 [SD, 14.0]; $U = 71.5$; $P = .023$) when correcting for multiple comparisons. Other sleep variables assessed using PSG revealed no differences among the three groups (see Table 1).

4. Discussion

Our study demonstrated that dopaminergic treatment in PD profoundly increases the secretion of melatonin. Moreover, although no differences in circadian phase (DLMO) or sleep timing (HSO) were found in PD compared to age-matched healthy controls, patients treated with dopaminergic therapy unexpectedly showed a delayed sleep onset relative to their DLMO. This finding suggests that dopaminergic therapy in PD results in uncoupling of circadian and sleep–wake regulation. This finding questions previous work showing a circadian phase advance in PD by recording plasma melatonin levels [12–14].

We observed differences between medicated PD and unmedicated PD patients on both the phase angle of entrainment and AUC despite these groups being matched for disease duration, stage, and motor severity. Specifically medicated PD patients had a significantly longer phase angle and greater melatonin output than the unmedicated PD group. Interestingly the unmedicated PD patients demonstrated similar results compared to controls on both of these measures, suggesting that the disease process itself may not be responsible for these changes. Furthermore, there was no difference in age, global cognition, depression, or use of antidepressant medications that could have formed an alternate explanation of these results.

The increased phase angle reported in the medicated PD group was not accompanied by evidence of insomnia. The medicated PD group reported the shortest SOL of the three groups. Other sleep variables collected during PSG indicated that the medication-related changes in the phase angle of entrainment and melatonin secretion were not accompanied by changes in sleep architecture.

The difference in phase angle of entrainment cannot be readily explained by a difference in DLMO or HSO times between the groups. Indeed the increased difference in HSO relative to DLMO in medicated patients, as indicated by the longer phase angle of entrainment, suggests that there may be an uncoupling or alterations in the internal phase relationships between the circadian rhythm of melatonin synthesis and the sleep–wake cycle. It is

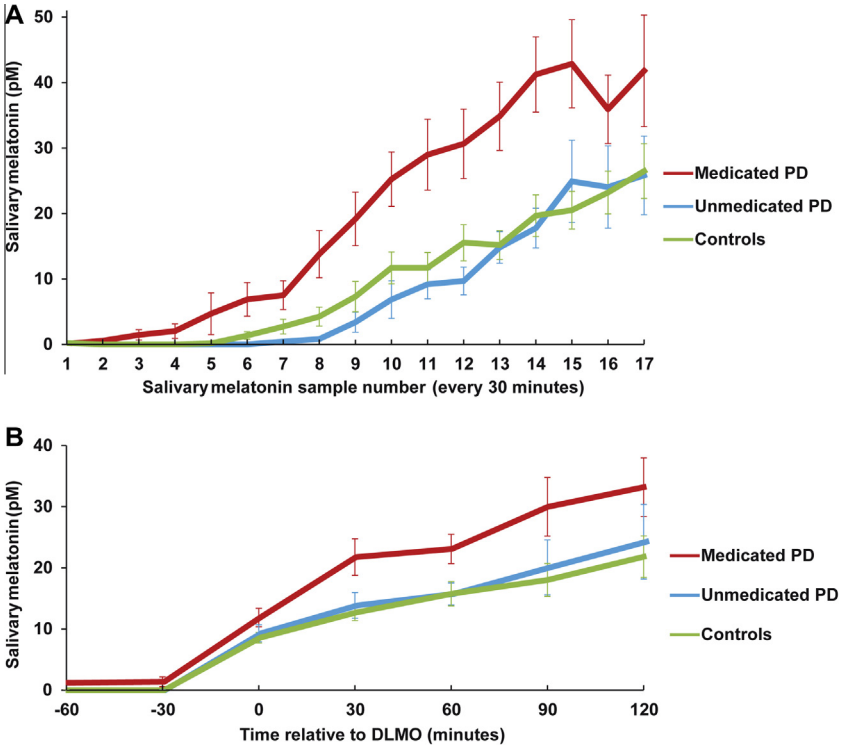

Fig. 3. Melatonin curve. A graph plotting the salivary melatonin levels (pM) (mean ± standard error) collected during the 8-h sampling period for patients with Parkinson disease (PD) who were medicated with dopaminergic replacement therapy, unmedicated patients with PD, and healthy age-matched controls. Panel A reports the increased area under the melatonin curve (AUC) in the medicated PD group compared to unmedicated PD and healthy age-matched controls, respectively. Panel B indicates that the increased AUC seen in the medicated PD group compared to unmedicated PD and controls, respectively, remained when the melatonin levels were plotted relative to their dim light melatonin onset time (DLMO).

possible that such alterations could account for some of the sleep disturbances noted in treated PD patients. For example, insomnia is more prevalent in patients with longer disease duration who are more likely to be taking doses of dopaminergic therapy [32].

Our results indicate that dopaminergic treatment rather than the neuropathology underlying PD is responsible for both the prolonged phase angle of entrainment and increased melatonin output level. However, despite matching for disease duration, stage, and motor severity it is possible that the assessment of medicated patients in their "on" state might have masked underlying neuropathologic deficits. This increased melatonin secretion in response to dopaminergic therapy may be related to recent findings linking dopamine to the regulation of the pineal gland. Animal models have identified the D4 dopamine receptor on the pineal gland [33]. Furthermore, the release of serotonin and melatonin from the pineal gland is reported to be controlled by circadian-related heterodimerization of adrenergic and dopamine D4 receptors [34].

Given the putative sleep-promoting properties of melatonin, the finding of an increased phase angle of entrainment in the presence of increased melatonin secretion would seem paradoxical [35]. Although establishing the neurochemical basis of these findings was beyond the scope of our study, our observation suggests that there may be some form of melatonin resistance among patients during the activation of their circadian systems and could account for the limited success of this therapy in PD patients with insomnia [36,37]. Alternatively it is possible that melatonin function follows an inverse U-shaped relationship similar to dopamine and serotonin, in which high levels can bring about paradoxical function. Further studies are needed to identify the mechanism affecting these phenomena.

Although melatonin levels were measured during the evening, these results raise the question of dopaminergic replacement therapy interfering with melatonin secretion during the day through similar pineal gland receptor-based mechanisms. Future studies using daytime melatonin sampling may be able to determine if the putative hypnotic properties of melatonin are implicated in the excessive daytime sleepiness seen in PD, which has previously been attributed to dopaminergic medication [32].

A relatively high number of participants in our study were excluded due to a sporadic melatonin profile from which DLMO could not be derived. The effects of sialorrhoea in PD combined with the reduced melatonin secretion accompanying aging could have contributed to this limitation [38]. Although 24-h melatonin sampling is not required to calculate the DLMO [39], an estimate of melatonin secretion over the entire circadian cycle would be more precise and should be considered in future work.

5. Conclusion

Our study suggests that, although there is no evidence of circadian phase change in PD, dopaminergic treatment profoundly affects the secretion of melatonin and the regulation of circadian phase and sleep timing. Studies are now needed to determine if these results contribute to specific sleep–wake disturbance in PD and to determine if these changes can be corrected with pharmacologic and nonpharmacologic approaches to help improve sleep in this common neurodegenerative disease.

Author contributions

Drafting/revising the manuscript for content, including medical writing for content; S.J. Bolitho, S.L. Naismith, S.M.W. Rajaratnam, R.R. Grunstein, J.R. Hodges, Z. Terpening, S.J.G. Lewis.

Study concept and design; S.J. Bolitho, S.L. Naismith, N. Rogers, S.J.G. Lewis.

Analysis and interpretation of data; S.J. Bolitho, S.L. Naismith, S.M.W. Rajaratnam, R.R. Grunstein, Z. Terpening, N. Rogers, S.J.G. Lewis.

Acquisition of data; S.J. Bolitho, Z. Terpening, N. Rogers.

Statistical analysis; S.J. Bolitho, S.L. Naismith, Z. Terpening.

Study supervision; S.L. Naismith, S.J.G. Lewis.

Obtaining funding; S.L. Naismith, N. Rogers, S.J.G. Lewis.

Funding sources

Funding of the study was supported by NHMRC PhD Scholarship and a CIRUS scholarship (S.J. Bolitho); NHMRC Career Development Award (S.L. Naismith); NHMRC Practitioner Fellowship (R.R. Grunstein); ARC Federation Fellowship (J.R. Hodges) NHMRC Practitioner Fellowship (S.J.G. Lewis). Dr S.M.W. Rajaratnam, Dr Z. Terpening and N. Rogers report no disclosures.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.10.016.

Acknowledgments

We acknowledge Professor David Kennaway for expertise with melatonin analysis.

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